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Contents:

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6007993
6245566
US   6090622A
DE  19525285A
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USPT,PGPB,JPAB,EPAB,DWPI	l15 and (toxicol$ or teratogen$)	0	L16
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USPT,PGPB,JPAB,EPAB,DWPI	l1 near15 (drug$1)	2	L4
USPT,PGPB,JPAB,EPAB,DWPI	l1 near15 (testing or assay$3)	11	L3
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USPT,PGPB,JPAB,EPAB,DWPI	embryoid adj bod$3	76	L1

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L13: Entry 18 of 19 File: DWPI Dec 1, 1999

DERWENT-ACC-NO: 1998-557073
DERWENT-WEEK: 200110

TITLE: New cells with characteristics of human pluripotent embryonic germ cells - used, e.g. to screen for specific modulators, drugs and toxins and for generating cells of selected lineage

ABTX:
Cells (A) having the characeristics of human pluripotent embryonic germ cells (EGC) are new. Also new are: (1) production of EGC by culturing human primordial germ cells (PCG) in presence of STO cells (ATCC CRL1503) in medium containing: (a) ligand (I) that binds to a receptor which can associate with gp130, or an antibody that binds to, and activates, gp 130, and (b) growth factor (GF), and (2) EGC produced this way.

ABTX:
USE - EGC are used (claimed): (i) to identify specific modulators (particularly compounds that inhibit or stimulate a cellular function); (ii) to produce cells with a restricted development lineage, particularly (neuro)endothelial cells or cardiomyocytes (but also haematopoietic progenitors as an alternative to bone marrow cells, and skeletal muscle cells); (iii) to produce immortalised cells of (ii) by expressing telomerase in them, and (iv) to identify agents that cause (de)-differentiation of EGC. Other uses include study of early human development; in transplants (e.g. for treating Parkinson's disease, for expressing receptors, ligands or neurotransmitters etc. (gene therapy) and to create neuronal networks or neuromuscular junctions); production of pharmaceuticals (insulin, factor VIII, antibodies); in biological sensors and for in vitro toxicological, mutagenic or teratogenic tests; to create cDNA libraries, and as in vitro models of human genetic disease.

ABEQ:
Cells (A) having the characeristics of human pluripotent embryonic germ cells (EGC) are new. Also new are: (1) production of EGC by culturing human primordial germ cells (PCG) in presence of STO cells (ATCC CRL1503) in medium containing: (a) ligand (I) that binds to a receptor which can associate with gp130, or an antibody that binds to, and activates, gp 130, and (b) growth factor (GF), and (2) EGC produced this way.

ABEQ:
USE - EGC are used (claimed): (i) to identify specific modulators (particularly compounds that inhibit or stimulate a cellular function); (ii) to produce cells with a restricted development lineage, particularly (neuro)endothelial cells or cardiomyocytes (but also haematopoietic progenitors as an alternative to bone marrow cells, and skeletal muscle cells); (iii) to produce immortalised cells of (ii) by expressing telomerase in them, and (iv) to identify agents that cause (de)-differentiation of EGC. Other uses include study of early human development; in transplants (e.g. for treating Parkinson's disease, for expressing receptors, ligands or neurotransmitters etc. (gene therapy) and to create neuronal networks or neuromuscular junctions); production of pharmaceuticals (insulin, factor VIII, antibodies); in biological sensors and for in vitro toxicological, mutagenic or teratogenic tests; to create cDNA libraries, and as in vitro models of human genetic disease.

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End of Result Set

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L13: Entry 19 of 19 File: DWPI Apr 5, 2001

DERWENT-ACC-NO: 1997-053732
DERWENT-WEEK: 200121

TITLE: Detecting embryo-toxic and teratogenic effects of chemicals - from their effects on stem cell or germ cell lines carrying reporter gene under control of tissue-specific promoter, eliminates need for animal testing

ABTX:
In vitro method for detecting chemical-induced embryo-toxicity/teratogenic effects based on differentiating, pluripotent embryonal stem cells (ESC) or embryonal germ cells (EGC) established from primordial germ cells of mice and rats, comprises:

ABTX:
(b) differentiation-dependent expression of tissue-specific genes from these clones in presence of teratogenic substances, active, at various times, during in vitro differentiation and subsequent differentiation into various germ line derivs., and

ABEQ:
In vitro method for detecting chemical-induced embryo-toxicity/teratogenic effects based on differentiating, pluripotent embryonal stem cells (ESC) or embryonal germ cells (EGC) established from primordial germ cells of mice and rats, comprises:

ABEQ:
(b) differentiation-dependent expression of tissue-specific genes from these clones in presence of teratogenic substances, active, at various times, during in vitro differentiation and subsequent differentiation into various germ line derivs., and

ABEQ:
In vitro method for detecting chemical-induced embryo-toxicity/teratogenic effects based on differentiating, pluripotent embryonal stem cells (ESC) or embryonal germ cells (EGC) established from primordial germ cells of mice and rats, comprises:

ABEQ:
(b) differentiation-dependent expression of tissue-specific genes from these clones in presence of teratogenic substances, active, at various times, during in vitro differentiation and subsequent differentiation into various germ line derivs., and

TTX:
DETECT EMBRYO TOXIC TERATOGENIC EFFECT CHEMICAL EFFECT STEM CELL GERM CELL LINE CARRY REPORT GENE CONTROL TISSUE SPECIFIC PROMOTE ELIMINATE NEED ANIMAL TEST

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L13: Entry 2 of 19 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245566 B1
TITLE: Human embryonic germ cell line and methods of use

ABPL:
Primordial germ cells isolated from human embryonic tissue, such as from the gonadal ridges of human embryo, are disclosed. The primordial germ cells are cultured resulting in cells that resemble embryonic stem cells or embryonic germ cells in morphology and pluripotency. The cells are maintained several months in culture and can be genetically manipulated using transgenic technology to insert heterologous genetic material.

BSPR:
Pluripotent embryonic stem cells have traditionally been derived principally from two embryonic sources. One type of mouse pluripotent cell can be isolated in culture from cells of the inner cell mass of a pre-implantation embryo and are termed embryonic stem (ES) cells (Evans & Kaufman, Nature 292: 154-156, 1981). A second type of mouse pluripotent stem cell can be isolated from primordial germ cells (PGCs) located in the mesenteric or genital ridges of days 8.5-12.5 post coitum mouse embryos and has been termed embryonic germ cell (EG) (Matsui et al., Nature 353:750-751, 1991; Resnick et al., Nature 359:550-551, 1992; Hogan, U.S. Pat. No. 5,453,357). Both types of cells are pluripotent and demonstrate germline genetic transmission in the mouse.

BSPR:
EG cells are derived from primordial germ cells (PGCs) cells isolated, according to one embodiment, from gonadal tissues, genital ridges, mesenteries or embryonic yolk sacs of human embryos. The PGCs are cultured under conditions that allow derivation of EG cells. The present invention also provides cell culture media for long term cell culture (more than 30 days) of the resulting EG cells.

DEPR:
"Embryonic germ cells" or "EG cells" are cells derived from primordial germ cells (PGCs). The term "embryonic germ cell" is used to describe cells of the present invention that exhibit an embryonic pluripotent cell phenotype. The terms "human embryonic germ cell (EG)" or "embryonic germ cell" can be used interchangeably herein to describe human cells, or cell lines thereof, of the present invention that exhibit a pluripotent embryonic stem cell phenotype as defined hereinbelow. Thus, EG cells are capable of differentiation into cells of ectodermal, endodermal, and mesodermal germ layers. EG cells can also be characterized by the presence or absence of markers associated with specific epitope sites identified by the binding of particular antibodies and the absence of certain markers as identified by the lack of binding of certain antibodies.

DEPR:
The term "primordial germ cells" (PGCs) is used to describe undifferentiated embryonic germ cells isolated over a period of time post-fertilization from anlagen or from yolk sac, mesenteries, or gonadal ridges of human embryos/fetus. PGCs are the source from which EG cells are derived. Gonocytes of later testicular stages also can be useful sources of PGCs.

DEPR:
In one embodiment, the invention provides human EG cells and a method of producing such cells. A starting material for isolating the cells may be primordial germ cells (PGCs) isolated over a period of about 9 weeks to about 11 weeks from the last menstrual period (LMP) (3-13 weeks post-fertilization), from embryonic yolk sac, mesenteries, gonadal anlagen, or genital ridges from human

embryos/fetus. Alternatively, gonocytes of later testicular stages can also provide PGCs. In one embodiment, the PGCs are cultured on mitotically inactivated fibroblast cells (e.g., STO cells) under conditions effective to derive EGs. The resulting human EG cells resemble murine ES or EG cells in morphology and in biochemical histotype. The resulting human EG cells can be passaged and maintained for at least several months in culture.

DEPR:
In another embodiment of the invention, EG cells or their differentiating or differentiated derivatives can be used for toxicological, mutagenic, and/or teratogenic in vitro tests and biosensors. These can replace various animal models, and form novel human based tests and extreme environment biosensors.

DEPR:
As previously described, in a preferred embodiment primordial germ cells (PGCs) are harvested from nascent gonadal ridges since their early developmental age inhibits subsequent differentiation and loss of pluripotency.

DEPR:
To ascertain that harvested cells were of an appropriate developmental age; harvested cells were tested for morphological criteria used to identify primordial germ cells that are pluripotent (DeFelici and McLaren, Exp. Cell. 142:476-482, 1982). To further substantiate pluripotency a sample of the extracted cells were subsequently tested for alkaline phosphatase (AP) activity. Markers for pluripotent cells are often useful to identify stem cells in culture. EG cells typically manifest alkaline phosphatase (AP) activity and AP positive cells are typically pluripotent. AP activity is rapidly lost with differentiation of EG cells in vitro. AP expression has been demonstrated in ES and ES-like cells in the mouse (Wobus et al., Exp. Cell 152:212-219, 1984; Pease et al., Dev. Bio. 141:344-352, 1990), rat (Ouhibi et al., Mol. Repro. Dev. 40:311-324, 1995), pig (Talbot et al., Mol. Repro. Dev. 36:139-147, 1993b) and cow (Talbot et al., Mol. Repro. Dev. 42:35-52, 1995). AP activity has also been detected in murine PGCs (Chiquoine, Anat. Rec. 118:135-146, 1954), murine EG cells (Matsui et al., Cell 70:841-847, 1992; Resnick et al., Nature 359:550-551, 1992), and cultured avian embryonic cells from chickens (Pain et al., Dev. 122:1996). In conjunction with morphological evaluation of the EG cell colony, AP expression therefore is a convenient marker to identify pluripotent embryonic germ cells in culture.

DEPR:
In the mouse, pluripotent embryonic stem cells are derived principally from two sources. Embryonic stem (ES) cells are derived from the inner cell mass of pre-implantation embryos, while embryonic germ (EG) cells are derived from primordial germ cells (PGCs) located in the genital ridge of day 8.5 to 12.5 post coitum embryo. Both types of cells are pluripotent and demonstrate germline genetic transmission in the mouse. Mouse ES and EG cells share several morphological characteristics such as high levels of intercellular alkaline phosphatase (AP), growth as tightly associated multicellular colonies, presentation of specific cell surface glycolipid and glycoprotein molecules. Some additional characteristics are a normal and stable karyotype and the ability to be continuously passaged. Embryonic stem cells that share some of these characteristics have been derived from avian species, mink, hamster, pig, bovine and the rhesus monkey.

DEPR:
Pluripotent embryonic stem cell lines have been derived from cultures of mouse primordial germ cells (PGCs), and have been referred to as EG (embryonic germ) cells. With the goal of establishing human EG cell lines, gonadal ridge and mesenteries of 5-9 week postfertilization embryos (obtained as the result of pregnancy termination) were cultured on mouse STO fibroblast feeder layers in the presence of a variety of growth factors, including human recombinant leukemia inhibitory factor (hrLIF), human recombinant basic fibroblast growth factor (hrbFGF), and forskolin. Initially, single PGCs were visualized by alkaline phosphatase (AP) staining. Over a period of 7-21 days, these PGCs gave rise to large multicellular colonies resembling those of early passage mouse EG and embryonic stem (ES) cell colonies. Throughout the culture period and with subsequent passages, the cells continued to be AP positive. The cells were also positive when tested against a panel of five monoclonal antibodies (SSEA-1, SSEA-3, SSEA-4, TRA-1-60 (ATCC HB-4783), TRA-1-81 (ATCC HB-4784)) used routinely to characterize pluripotent stem cells. The cultured cells have been continuously

passaged and found to be karyotypically normal and stable. Both XX and XY cell cultures have been obtained. The properties so far characterized on the derived human cells are consistent with those anticipated for pluripotent stem cells. (See Table 2)

DEPC:
Collection of Human Primordial Germ Cells and Derivation of Embryonic Germ Cells

CLPR:
1. A method for producing human pluripotent embryonic germ (hEG) cells, comprising culturing human primordial germ cells (PGCs) in a culture medium comprising:

CLPR:
27. A method for producing and maintaining human pluripotent embryonic germ (hEG) cells, comprising culturing human primordial germ cells (PGCs) in a culture medium comprising:

CLPR:
28. A method for producing human pluripotent embryonic germ (hEG) cells, comprising culturing human primordial germ cells (PGCs) in a culture medium comprising:

ORPL:
Moore, K., "Characterization of Porcine Inner Cell Mass (plCM) and Primordial Germ Cells (pPGC) for the Development of Transgenic Embryonic Cell Lines", Diss. Abst. International--B, vol. 58, No. 11, Order No. DA9815812, May 1998.*

ORPL:
Durcova-Hills et al., "Short-Term Culture of Porcine Primordial Germ Cells", Theriogenology, vol. 49, No. 1, p. 237, 1998.*

ORPL:
Labosky et al., "Embryonic germ cell lines and their derivation from mouse primordial germ cells" Germline Development (Ciba Foundation Symposium 182) p. 157-158 (1994).

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L13: Entry 10 of 19 File: USPT Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6007993 A
TITLE: In vitro test for embryotoxic and teratogenic agents using differentiation-dependent reporter expression in pluripotent rodent embryonic cells

BSPR:
The invention relates to an in vitro test procedure for the detection of chemically-induced embryotoxic (for example also teratogenic) effects based on differentiated pluripotent embryonic stem (ES) cells from the mouse and rat and using embryonic germ (EG) cells obtained established from primordial germ cells.

BSPR:
The detection of teratogenic properties of chemical agents occurs at this time by determination of the reproduction toxicity of test substances following single or multi-administrations to pregnant laboratory mammals and by tests of the embryotoxicity in the early stages of pregnancy (Holz and Siegemund, "Der Einsatz von Tieren in der Forschung und Entwicklung im Verbraucher- und Umweltschutz, Abschlussbericht zur Basiserhebung des Batelle-Instituts 1988 {The Use of Animals in the Research and Development in the Protection of the Consumer and the Environment, Final Report to the Base Determination of the Batelle Institute 1988}). Furthermore, in vitro tests are performed with mammal embryos (Neubert and Merker, Cell culture techniques--applicability for studies on prenatal differentiation and toxicity, de Gruyter, Berlin--New York (1981)) and with embryonic organs for teratogenicity tests. These tests procedures have however the disadvantage that they require the use of a large number of live mammals, in particular rats and mice. In vitro test procedures, in which primary cell cultures of limb buds (for example, "Limb Buds", Kochhar, Teratology 11, 273-287 (1975)), or brain parts of embryonic rats (Flint and Orton, Toxicol. Appl. Pharmacol. 76, 383-395 (1984)) or permanent cell lines of embryonic or adult mammal tissue, such as tumor cells of the ovary or embryonic palate cells are employed, do not fulfill, strictly speaking, the requirements which are imposed on the teratogenicity tests during the embryogenesis, namely giving indications of possible disgeneses or developmental disturbances.

BSPR:
Efforts have been made for a couple of years to employ permanent cultures of totipotent/pluripotent embryonic stem cells (ES cells) for the detection of embryotoxic and mutagenic substances (Laschinski et al., Reproductive Toxicol. 5, 57-65 (1991), Newall and Beedles, Toxicol. in Vitro 8, 697-701 (1994), Sehlmeyer and Wobus, Mutation Res. 324, 69-76 (1994)). Embryonic stem cells are the totipotent cells of the early embryo from which there develops the complete mammal organism. Disturbances during the germ-layer and prenatal development can lead to the necrosis of the embryos (preimplantative death), to developmental disturbances, maldevelopment or, respectively, malformations.

BSPR:
It has been demonstrated in previous experiments that the teratogenic retinoic acid (RA) led to grave changes of the expression of tissue-specific genes if it took effect at specific times of the embryoid body differentiation, and to activation, repression, or modulation of the expression of the myocardial-specific genes or somatic-specific genes (Wobus et al., Roux's Arch. Dev. Biol. 204, 1994 (36-45). This activation, repressing, or modulation of the gene expression can also be made visible through reporter genes, for example X-Gal or luciferase.

BSPR:

Tests relative to the cytotoxicity with the aid of the stem cell tests for detecting teratogenic activity were described by Newall and Beedles, Toxicol. in Vitro 8, 697-701 (1994).

BSPR:
Cytotoxic effects served in all of these tests as a measure for embryocidal properties of teratogenic/embryotoxic substances.

BSPR:
It is noted that ES cells are at this time the most important cell model in the developmental biology, particularly for the construction of transgenic organisms, however, its employment in the reproduction toxicology and gene toxicology is up to now limited.

BSPR:
The object of the invention resides in developing an in vitro test procedure for the detection of embryotoxic/teratogenic properties of chemical agents relative to embryonic stem (ES) cells or relative to embryonic germ (EG) cells associated with primordial germ cells. The test procedure is to be particularly suited to give indications of possible developmental disturbances and differentiation disturbances during the embryogenesis.

BSPR:
According to the present invention there is provided an in vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem (ES) cells or embryonic germ (EG) cells obtained from primordial germ cells of the mouse and rat. The procedure includes the following steps. Stable transgenic ES/EG cell clones are selected. A differentiation-dependent expression of tissue-specific genes of embryonic stem (ES) cell clones or embryonic germ (EG) cell clones is furnished in the presence of teratogenic substances. Said teratogenic substances act at specific times of the in vitro differentiation and subsequent differentiation. A chemically-induced activation, repression or modulation of the tissue-specific genes which influence embryonic development is detected.

BSPV:
2. embryonic germ cells (embryonic germ cells, EG cells), which are obtained from primordial germ cells (PGC) of about 9-day old embryos and are cultivated as permanent cell lines (Stewart et al., Dev. Biol. 161, 626-628 (1994)).

DRPR:
FIG. 2A is a X-Gal staining without induction through the teratogenic substance RA;

DEPR:
Stable transgenic ES or EG stem cell clones are constructed, wherein a bacterial reporter gene LacZ or the luciferase gene is brought under the control of tissue-specific promoters or developmental control genes. Following differentiation of the ES cells in the presence of teratogenic substances into the different germination path derivatives, there occurs a differentiation-dependent expression in the cells, which expresses the tissue-specific promoters. The activation, repression or modulation of these tissue-specific genes is detected based on a simple staining reaction, the X-Gal assay. A battery of relevant test ES cell clones are developed with the invention, wherein the test ES cell clones contain promoter sequences in addition to the reporter gene LacZ (and a neomycin cassette for the selection of stable transfectants), where the promoter sequences regulate characteristic and essential features of the ectodermal and mesodermal line. It should in particular be genes which determine the neuronal, cardiogenic, the muscle, and the skeletal development. Following transfection of these vectors in pluripotent ES/EG cells of the mouse or the rat, stable stem cell clones are selected and these are differentiated after embryoid body development at specific times in the absence of test substances (FIG. 1). Following thereto, the differentiation-dependent expression of the tissue-specific gene can be proven with the aid of the X-Gal staining at different developmental states (while maintaining time and employing vectors suitable therefor). This staining technique can be standardized and can be automated with photometric procedures.

DEPR:

The substantial advantage of the invention resides in that a standardizable in vitro model is established in a routine screening, wherein the in vitro model leads to a saving of test animals. About 20,000 mammals and birds were used in the field of the reproduction toxicology in Germany per year (1987). Above and beyond this, a large number of mammals are needed for the removal of embryonic organs and tissue (embryonic myocardial cells, limb bud cultures, micromass assay, and the like) such that the total of animal numbers could be at least at 50,000.

DEPR:
FIG. 2A, FIG. 2B, and FIG. 2C show the activation of the MLC-2V expression in the MLC clone 3 by 10.sup.-8 M, FIG. 2C, and 10.sup.-9 M, FIG. 2B, RA after treatment between the 5th and 15th day of the embryoid body differentiation. The control cells FIG. 2A, show X-Gal staining without induction through the teratogenic substance RA.

CLPR:
1. In vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem (ES) cells or embryonic germ (EG) cells obtained from primordial germ cells of a mouse and rat comprising the steps of:

CLPR:
19. In vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem (ES) cells or embryonic germ (EG) cells obtained from primordial germ cells of the mouse and rat, comprising the steps of:

CLPV:
furnishing a differentiation-dependent expression of tissue-specific genes of embryonic stem (ES) cell clones or embryonic germ (EG) cell clones in the presence of teratogenic substances, said teratogenic substances acting at specific times of an in vitro differentiation, and subsequent differentiation, and

CLPV:
expressing tissue-specific genes of embryonic stem (ES) cell clones or embryonic germ (EG) cell clones differentiation-dependently in the presence of teratogenic substances, wherein said teratogenic substances are acting at specific times of an in vitro differentiation;

CLPV:
basing the procedure on differentiated pluripotent embryonic stem (ES) cells or embryonic germ (EG) cells obtained from primordial germ cells of the mouse or rat.

CLPV:
expressing tissue-specific genes of embryonic stem (ES) cell clones or embryonic germ (EG) cell clones in vitro differentiation-dependent in the presence of embryotoxic or teratogenic chemical substances;

CLPV:
detecting an embryotoxic or teratogen-induced activation, repression or modulation of tissue-specific genes, which influence embryonic development.

CLPV:
furnishing a differentiation-dependent expression of tissue-specific genes of embryonic stem (ES) cell clones or embryonic (EG) cell clones in the presence of teratogenic substances, said teratogenic substances acting at specific times of an in vitro differentiation, and subsequent differentiation; and

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L8: Entry 6 of 7 File: USPT Oct 13, 1998

DOCUMENT-IDENTIFIER: US 5821121 A
TITLE: Hormone-secreting cells maintained in long-term culture

BSPR:
Toxicity testing is another field which scientists have attempted to address through use of in vitro systems (for review see: Nau, H. 1990, in Methods in Developmental Toxicology: Use in Defining Mechanisms and Risk Parameters. Eds. G. L. Kimmel, D. M. Kochhar, CRC Press, pp. 29-43.) To date, in vitro systems based on hormone-secreting cells have been very limited, partly because of the difficulties inherent in maintaining hormone-secreting cells in culture. In theory, the reproductive toxicity of a compound could be assessed by the capacity of the compound to impair hormone-secretion from cells which characteristically secrete a given hormone. A on-human cell line (Chinese hamster ovary, CHO) has been extensively utilized for toxicology analyses, (Tsushimoto, G., et al., 1983 Arch Environ Contam Toxicol 12:721). Amphibian oocytes have been proposed as a system for the testing of tumor promoting compounds (U.S. Pat. No. 4,983,527; issued Jan. 8, 1991). Xenopus testis explants have been proposed for the testing of mutagenicity and genotoxicity during spermatogenesis (U.S. Pat. No. 4,929,542; issued May 29, 1990). Cell lines established from rat embryo fibroblasts have been proposed as systems for screening for protein inhibitors and activators (U.S. Pat. No. 4,980,281; issued Dec. 25, 1990). Since it is generally recognized that humans have different toxic susceptibilities compared to amphibians and rodents, the above proposed in vitro testing systems are limited by the non-human origins of the cells.

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L8: Entry 5 of 7 File: USPT Dec 15, 1998

DOCUMENT-IDENTIFIER: US 5849995 A
TITLE: Mouse model for Huntington's Disease and related DNA sequences

DEPR:
Homozygous HD mice serve as models to study embryogenesis and development. HD homozygous mutant embryos die during early post-implantation. These embryos could be recovered and portions cultured in vitro in the presence of novel drugs designed to compensate for the lack of HD gene product in these embryos. Drug testing in these mice could lead to the development of drugs which could rescue early embryos normally aborted.

L8: Entry 4 of 7 File: USPT Jul 27, 1999

DOCUMENT-IDENTIFIER: US 5928942 A
TITLE: Hormone-secreting cells derived from pancreatic islet maintained in long-term culture

BSPR:
Toxicity testing is another field which scientists have attempted to address through use of in vitro systems (for review see: Nau, H. 1990. in Methods in Developmental Toxicology: Use in Defining Mechanisms and Risk Parameters. Eds. G. L. Kimmel, D. M. Kochhar, CRC Press, pp. 29-43.) To date, in vitro systems based on hormone-secreting cells have been very limited, partly because of the difficulties inherent in maintaining hormone-secreting cells in culture. In theory, the reproductive toxicity of a compound could be assessed by the capacity of the compound to impair hormone-secretion from cells which characteristically secrete a given hormone. A non-human cell line (Chinese hamster ovary, CHO) has been extensively utilized for toxicology analyses, (Tsushimoto, G., et al., 1983 Arch Environ Contam Toxicol 12: 721). Amphibian oocytes have been proposed as a system for the testing of tumor promoting compounds (U.S. Pat. No. 4,983,527; issued Jan. 8, 1991). Xenopus testis explants have been proposed for the testing of mutagenicity and genotoxicity during spermatogenesis (U.S. Pat. No. 4,929,542; issued May 29, 1990). Cell lines established from rat embryo fibroblasts have been proposed as systems for screening for protein inhibitors and activators (U.S. Pat. No. 4,980,281; issued Dec. 25, 1990). Since it is generally recognized that humans have different toxic susceptibilities compared to amphibians and rodents, the above proposed in vitro testing systems are limited by the non-human origins of the cells.

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L8: Entry 3 of 7 File: USPT Aug 3, 1999

DOCUMENT-IDENTIFIER: US 5932418 A
TITLE: Fish embryo screening test for genotoxic agents using three different developmental life stages

BSPR:
Toxicologists have also displayed interest, albeit limited, in the use of intact embryos in toxicity testing. For example, in assays for apoptosis as induced by various physical and chemical environmental factors, there have been only two published reports employing embryos. In these reports, gestational day 10-11 rat conceptuses and preimplantation rabbit embryos have been evaluated for susceptibility to apoptosis in response to peptidyl diazomethanes and radiation, respectively. See Ambroso J L and Harris C. Teratology 50(3):214-228 (1994); Hegele-Hartung, C., et al., Anat. Embryol. (Berlin) 178 (3):229-241 (1988). The lack of widespread use of whole embryos in testing for environmentally-induced apoptosis may testify to the technical difficulties of research using in vitro testing of whole mammalian embryos.

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L8: Entry 2 of 7 File: USPT Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5981165 A
TITLE: In vitro induction of dopaminergic cells

BSPR:
For some purposes, especially transplantation and certain drug testing procedures, it would be advantageous to use completely defined culture conditions to induce the differentiation of dopaminergic cells. It would be particularly advantageous if the cells were obtained from both dopaminergic and normally non-dopaminergic neural tissue sources, thus maximizing the number of dopaminergic cells that can be generated from a single embryo.

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L8: Entry 1 of 7 File: USPT Aug 8, 2000

DOCUMENT-IDENTIFIER: US 6100089 A
TITLE: Rapid screening mutagenesis and teratogenesis assay

BSPR:
Toxicity testing is required for many new drugs and agents released into the environment or work place. Compounds must generally be screened for damage to the embryo (teratogenesis activity) and for damage to the differentiated animal (carcinogenesis or mutagenesis activity).

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L11: Entry 4 of 40 File: USPT Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6140121 A
TITLE: Methods and compositions to improve germ cell and embryo survival and function

DRPR:
FIGS. 11A-11D are flow cytometry profiles of DNA from sperm frozen with PCAGH (A) and (B) or egg yolk buffer (C) and (D) extenders.

DEPR:
In other aspects of this invention, methods are provided for increasing the survival of oocytes, embryos or embryonic stem cells (ESC) in in vitro culture systems. Oocytes, embryos, or ESC are cultured for use in various diagnostic and toxicology assays, in vitro fertilization, or for the propagation of offspring. These methods comprise contacting a sample containing an oocyte, an embryo or ESC with a culture medium that includes a PCAGH.

L11: Entry 13 of 40 File: USPT Aug 3, 1999

DOCUMENT-IDENTIFIER: US 5932418 A
TITLE: Fish embryo screening test for genotoxic agents using three different developmental life stages

BSPR:
Toxicologists have also displayed interest, albeit limited, in the use of intact embryos in toxicity testing. For example, in assays for apoptosis as induced by various physical and chemical environmental factors, there have been only two published reports employing embryos. In these reports, gestational day 10-11 rat conceptuses and preimplantation rabbit embryos have been evaluated for susceptibility to apoptosis in response to peptidyl diazomethanes and radiation, respectively. See Ambroso J L and Harris C. Teratology 50(3):214-228 (1994); Hegele-Hartung, C., et al., Anat. Embryol. (Berlin) 178 (3):229-241 (1988). The lack of widespread use of whole embryos in testing for environmentally-induced apoptosis may testify to the technical difficulties of research using in vitro testing of whole mammalian embryos.

BSPR:
Fish embryos, both marine (herring, mackerel) and freshwater (rainbow trout, zebrafish) have been used in the past by aquatic toxicologists. The biomarkers used in these fish embryo toxicity assays can be summarized according to the following Table (THIS=this invention; n.a.=not applicable; [#]=prior art reference discussed below; none=no prior art reference found).

BSPR:
The above table presents a conceptual framework for analysis of prior art for fish embryo bioassays. Papers [1] and [2] are representative of a class of papers which scores very broad and non-specific defects (such as lethality and teratogenicity, or body-pattern defects). For example, [1] refers to a study where ten chemicals were screened against both the RTG-2 (rainbow trout gonad) cell line in a live/dead test and against zebrafish embryos, up to 96 hours of age, for lethality and for teratogenic (body-patterning) defects. See Lange M. et al. Chemosphere 30, 2087-2102 (1995). In reference [2], rainbow trout eggs were injected with halogenated aromatic hydrocarbons and the mortality at hatching was measured. See Walker et al. Aquat. Toxicol. 22: 15-38 (1992). The above Table shows that this class of papers in fact does not overlap with the claims of the present invention.

BSTL:
TABLE I Summary of Prior Art: Fish Embryo Tests. TESTING ENDPOINT fish embryo cytogenetic life-stage lethality teratogenicity apoptosis defects embryo: pre MBT [1, 2] n.a. none THIS; [3, 4, 5] embryo: MBT [1, 2] n.a. none THIS; [3, 4, 5] to mid-gastrula embryo: mid-late [1, 2] [1] THIS THIS; [3, 4, 5] gastrula embryo: [1, 2] [1] none none somitogenesis embryo: [1, 2] [1] none none organogenesis

CLPV:
(h) correlating said frequencies with the presence and efficacy of a genotoxic agent using an empirical database based on genotoxic standards.

L11: Entry 39 of 40 File: USPT Sep 27, 1988

DOCUMENT-IDENTIFIER: US 4774248 A
TITLE: Methods of treating depression and depressive states using 5-phenyl-1,4,5,6-tetrahydropyrimidine derivatives

BSPR:
From the article by D. G. UPSHALL, Teratology, 5 (No. 3), pages 287-294, (1972), it is known that phenyl-1,4,5,6-tetrahydropyrimidine derivatives, in which the phenyl group is located in the 2, 3 (sic), 4, 5 or 6 position [see Table 1, page 288, and page 289, right-hand column, lines 22-26], have been prepared and tested for possible teratogenic properties on chicken embryos.

BSPR:
In other words, the above-mentioned article by D. G. UPSHALL does not describe the compounds according to the invention, of the formula I below, or their use in therapy as substances which act on the CNS. At most, this article refers to the absence of teratogenic effects on chicken embryos of an isomer (the said compound No. 18 mentioned above) of a product according to the invention (CRL 41 336, the subject of Example 1 below).

BSPR:
The compounds of the formula I according to the invention share the property of acting on the CNS. In their neuropsychopharmacological profile, they display in particular antidepressant and sedative effects of greater or lesser intensity. More precisely, (i) the compounds of the formula I.sub.c act mainly as sedatives and possess relatively unpronounced antidepressant effects; on the other hand, (ii) the compounds of the formulae I.sub.a and I.sub.b display mainly antidepressant effects on the CNS and, to a minor extent, sedative effects which become apparent at high doses. The compounds of the formula I.sub.a also display peripheral .alpha.-adrenergic stimulant properties, as will be seen below. The compounds of the formulae I.sub.a and I.sub.b are particularly valuable in therapy as antidepressant substances.

DEPR:
The results of the tests undertaken show that, in its neuropsychopharmacological profile, CRL 41 378 has:

DEPR:
The results of the tests summarized above show that, in its neuropsychopharmacological profile, CRL 41 382 has:

DEPR:
The general profile of the activity of CRL 41 382 in animals makes this substance resemble .beta.-adrenergic stimulants. In fact, the absence of peripheral anticholinergic activity and the absence of antagonism of the immobility due to "despair" distinguish CRL 41 382 from imipramine antidepressants. The absence of stimulant effects distinguishes CRL 41 382 from stimulant antidepressants such as nomifensin, amineptin or even amphetamine. Finally, the absence of antagonism of the ptosis induced by reserpine and the speed with which the effects of CRL 41 382 appear enable it to be distinguished from monoamine oxidase inhibitors.

DEPR:
It is found that, in its neuropsychopharmacological profile, CRL 41 329 has:

DEPR:
It is found that, in its neuropsychopharmacological profile, CRL 41 352 has:

DEPR:
The results of the tests undertaken show that, in its neuropsychopharmacological profile, CRL 41 336 has:

DEPR:
The results of the tests undertaken show that, in its neuropsychopharmacological profile, CRL 41 337 has:

DEPR:
In summary, as regards the results of the tests undertaken, CRL 41 337 behaves like a substance which acts principally as an antidepressant. Certain aspects of its neuropsychopharmacological profile resemble those of .beta.-adrenergic stimulants (antagonism of the hypothermia induced by apomorphine, reserpine and oxotremorine, but with no effect in the test for measuring the immobility due to despair). Finally, CRL 41 337 differs from imipramine substances by the fact that it has no anticholinergic action and no effect on the immobility due to despair, on the one hand, and from antidepressants, such as nomifensin, by the fact that it exhibits no stimulation of the spontaneous motor activity, on the other.

DEPR:
Using this procedure, it is found that the test products differ in their neuropsychopharmacological profiles from tricyclic antidepressants (such as desipramine), amphetamines (such as amphetamine itself) and serotonin release agents (such as fenfluramine), which potentiate all the effects of 5-HTP in the presence of an MAOI. On the other hand, the said products more closely resemble .beta.-adrenergic stimulants, which exert disparate effects towards 5-HTP, such as isoprenaline (distinct potentiation of the trembling and head twitches), fenoterol (distinct potentiation of the trembling and moderate potentiation of the head twitches), ritodrine and, to a lesser extent, salbutamol (moderate potentiation of the trembling but no modification of the head twitches) and terbutaline and ociprenaline (no modification of the trembling or head twitches).

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L11: Entry 40 of 40 File: USPT Dec 12, 1978

DOCUMENT-IDENTIFIER: US 4129643 A
TITLE: Method for rapid screening of teratogenic agents

BSPR:
Current tests of new drugs and other agencies for possible teratogenic effects on the human foetus are slow and expensive. Such tests are generally performed by the examination of some thousand rodent foetuses of various ages from pregnant females injected or fed with suspected teratogenic substances at different stages of pregnancy and at different dose levels. Other mammals are sometimes used. The embryos are examined for morphopathology and for hisopathology. Different periods of foetal sensitivity and different levels of susceptibility between strains and species characterise the response to teratogenic agencies. For this reason some investigations have used more than one species. Nevertheless the applicability of tests on rodents etc. to effects expected in man must always remain in doubt, since there are differences in placental structure and physiology as well as pharmacogenetic differences between species, yet tests on primates are even more expensive and time consuming than rodent tests, and are therefore not often undertaken.

BSPR:
(3) An assay method which is rapid, repeatable, objective and quantitative is provided by the measurement of the profiles of accumulation and synthesis of individual proteins of the test cells (the synthesis being measured after incorporation of radioactive precursors before harvesting), as demonstrated by the densitometric quantitation (using any suitable accurate commercial densitometer) of the cell contents after resolution by high-resolution separation, e.g. by isoelectric focussing in polyacrylamide gels or other stabilising media in dissociating conditions (e.g. by using 6-8M urea) and staining with any of the quantitative protein stains (or in principle by absorbance at appropriate wavelength with unstained material). Similar densitometry is made of the autoradiograph of the gels. Each analysis can be done on a culture grown from a cell suspension of as little as 1-4.5 .times. 10.sup.5 cells, but can be scaled up or down as required.

DEPR:
The protein profile of the lens epithelial cells grown in medium containing amniotic fluid is the same as that in medium without amniotic fluid. Cells grown in amniotic fluid from mice injected with 6-aminonicotinamide had a modified cell outline and a consistent set of changes in the protein profile, one band being missing and one exaggerated; while some other, less striking quantitative changes were also recorded. A few were probably no greater than random fluctuations, but many were seen regularly. Cells grown in amniotic fluid from mice injected with sodium acetyl salicylate are normal in morphology (unless they and their controls are grown in sub-optimal conditions). In all cases they were lacking in the band which was enhanced by 6-aminonicotinamide treatment. Other quantitative changes were also observed. Quantitative changes in the autoradiograph traces were found which distinguish equally well between the effects of these two drugs. Changes in the stained gels indicate changes in accumulated protein, those in the autoradiographs, changes in protein synthesis. These changes are presumably related to each other.

CLPR:
4. A process as claimed in claim 1 wherein the profiles of accumulation and synthesis of individual proteins of the cells being cultured are measured, the synthesis being measured after incorporation of radioactive precursor before harvesting.

harvesting.

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USPT,PGPB,JPAB,EPAB,DWPI	l6 same (embryonic or embryo$1)	7	L8
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USPT,PGPB,JPAB,EPAB,DWPI	(drug adj testing) or (toxicity adj testing)	1083	L6
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USPT,PGPB,JPAB,EPAB,DWPI	l1 near15 (drug$1)	2	L4
USPT,PGPB,JPAB,EPAB,DWPI	l1 near15 (testing or assay$3)	11	L3
USPT,PGPB,JPAB,EPAB,DWPI	l1 near15 (toxic$)	1	L2
USPT,PGPB,JPAB,EPAB,DWPI	embryoid adj bod$3	76	L1

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L14: Entry 1 of 1 File: USPT Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6007993 A
TITLE: In vitro test for embryotoxic and teratogenic agents using differentiation-dependent reporter expression in pluripotent rodent embryonic cells

BSPR:
The invention relates to an in vitro test procedure for the detection of chemically-induced embryotoxic (for example also teratogenic) effects based on differentiated pluripotent embryonic stem (ES) cells from the mouse and rat and using embryonic germ (EG) cells obtained established from primordial germ cells.

BSPR:
According to the present invention there is provided an in vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem (ES) cells or embryonic germ (EG) cells obtained from primordial germ cells of the mouse and rat. The procedure includes the following steps. Stable transgenic ES/EG cell clones are selected. A differentiation-dependent expression of tissue-specific genes of embryonic stem (ES) cell clones or embryonic germ (EG) cell clones is furnished in the presence of teratogenic substances. Said teratogenic substances act at specific times of the in vitro differentiation and subsequent differentiation. A chemically-induced activation, repression or modulation of the tissue-specific genes which influence embryonic development is detected.

L13: Entry 2 of 19 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245566 B1
TITLE: Human embryonic germ cell line and methods of use

ABPL:
Primordial germ cells isolated from human embryonic tissue, such as from the gonadal ridges of human embryo, are disclosed. The primordial germ cells are cultured resulting in cells that resemble embryonic stem cells or embryonic germ cells in morphology and pluripotency. The cells are maintained several months in culture and can be genetically manipulated using transgenic technology to insert heterologous genetic material.

BSPR:
Pluripotent embryonic stem cells have traditionally been derived principally from two embryonic sources. One type of mouse pluripotent cell can be isolated in culture from cells of the inner cell mass of a pre-implantation embryo and are termed embryonic stem (ES) cells (Evans & Kaufman, Nature 292: 154-156, 1981). A second type of mouse pluripotent stem cell can be isolated from primordial germ cells (PGCs) located in the mesenteric or genital ridges of days 8.5-12.5 post coitum mouse embryos and has been termed embryonic germ cell (EG) (Matsui et al., Nature 353:750-751, 1991; Resnick et al., Nature 359:550-551, 1992; Hogan, U.S. Pat. No. 5,453,357). Both types of cells are pluripotent and demonstrate germline genetic transmission in the mouse.

BSPR:
EG cells are derived from primordial germ cells (PGCs) cells isolated, according to one embodiment, from gonadal tissues, genital ridges, mesenteries or embryonic yolk sacs of human embryos. The PGCs are cultured under conditions that allow derivation of EG cells. The present invention also provides cell culture media for long term cell culture (more than 30 days) of the resulting EG cells.

DEPR:
"Embryonic germ cells" or "EG cells" are cells derived from primordial germ cells (PGCs). The term "embryonic germ cell" is used to describe cells of the present invention that exhibit an embryonic pluripotent cell phenotype. The terms "human embryonic germ cell (EG)" or "embryonic germ cell" can be used interchangeably herein to describe human cells, or cell lines thereof, of the present invention that exhibit a pluripotent embryonic stem cell phenotype as defined hereinbelow. Thus, EG cells are capable of differentiation into cells of ectodermal, endodermal, and mesodermal germ layers. EG cells can also be characterized by the presence or absence of markers associated with specific epitope sites identified by the binding of particular antibodies and the absence of certain markers as identified by the lack of binding of certain antibodies.

DEPR:
The term "primordial germ cells" (PGCs) is used to describe undifferentiated embryonic germ cells isolated over a period of time post-fertilization from anlagen or from yolk sac, mesenteries, or gonadal ridges of human embryos/fetus. PGCs are the source from which EG cells are derived. Gonocytes of later testicular stages also can be useful sources of PGCs.

DEPR:
In one embodiment, the invention provides human EG cells and a method of producing such cells. A starting material for isolating the cells may be primordial germ cells (PGCs) isolated over a period of about 9 weeks to about 11 weeks from the last menstrual period (LMP) (3-13 weeks post-fertilization), from embryonic yolk sac, mesenteries, gonadal anlagen, or genital ridges from human

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L8: Entry 7 of 7 File: DWPI Nov 13, 1997

DERWENT-ACC-NO: 1997-551508
DERWENT-WEEK: 199751

TITLE: Vector for specific gene expression in vascular smooth muscle - contains smooth muscle myosin heavy chain gene promoter

ABTX:
USE - The vector system can be used to create a transgenic animal model by gene addition or deletion, modify embryonic stem cells, express a marker gene for the selection and/or immortalisation of vascular smooth muscle cells from embryonic stem cells (especially to create an in vitro model for drug toxicity testing, or obtain cells that can be transfected with a shuttle vector containing 1 or more therapeutic genes ex vivo before being transplanted into an organism for cell mediated gene transplantation or somatic gene transfer), target expression of therapeutic DNA for disease treatment and for gene therapy by administration via the bloodstream, preferably by administration into the coronary venous or arterial system through a catheter.